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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
|---|---|---|---|
| 08/994,468 | 12/19/97 | LYMAN S | 2813-L |

HM22/0814

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| EXAMINER | |
|---|---|
| KERR, J | |
| **ART UNIT** | **PAPER NUMBER** |
| 1633 | 14 |

**DATE MAILED:** 08/14/00

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trad marks**

# Office Action Summary

| Application No. | Applicant(s) |
|---|---|
| 08/994,468 | Lyman et al. |
| **Examiner** | **Group Art Unit** |
| Janet M. Kerr | 1633 |

☒ Responsive to communication(s) filed on *May 26, 2000*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claims**

☒ Claim(s) *1-30* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-30* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

**Application Papers**

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

*--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---*

### *Continued Prosecution Application*

The request filed on 5/26/00 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/994,468 is acceptable and a CPA has been established. An action on the CPA follows.

Applicants' amendment, filed on 5/26/00, has been entered.

Claims 1-30 are pending.

### *Specification*

The disclosure is objected to because of the following informalities: on page 38, Table I, the numbers correlating with cpm should be placed in the appropriate positions under the column headings.

Appropriate correction is required.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for primitive hematopoietic cell expansion media comprising the full length flt-3 ligand or flt-3 ligand and other growth factors such as a soluble polypeptide that comprises an amino acid sequence that is identical to the amino acids 28-160 of SEQ ID NO:6, and a method of culturing the primitive hematopoietic cells in the expansion media, does not reasonably provide enablement for hematopoietic cell expansion media, *per se*, or hematopoietic cell

expansion media comprising a soluble polypeptide that comprises an amino acid sequence that is at least 80% identical to the amino acids 28-160 of SEQ ID NO:6. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-30 are directed to hematopoietic cell expansion media and methods of culturing hematopoietic cells in the expansion media. While the specification is enabling for media and cell culture methods which require the media for expanding primitive hematopoietic cells, the specification is not enabling for culturing any and all hematopoietic cells with the media, or media for expanding any and all hematopoietic cells.

The specification discloses media and methods of culturing AA4.1+ fetal liver cells and c-kit-positive cells by compositions containing flt3-L and IL-3 or IL-7 (see, e.g., pages 36 and 37) such that the AA4.1+ fetal liver cells and c-kit-positive hematopoietic cells proliferate *in vitro*. However, the specification does not disclose that hematopoietic cells of a more differentiated phenotype can proliferate in the presence of flt3-L and additional cytokines, such as IL-3 or IL-7, under *in vitro* culture conditions.

It is well known that hematopoietic cell populations respond differently to cytokines. The unpredictability of formulating a media composition for proliferating hematopoietic cells *in vitro* is recognized in the art at the time of filing. As one example, Lyman *et al.* (Cell, 75:1157-1167, 1993) teach that cell culture media comprising flt-3 ligand and cytokines such as IL-7 and SLF are capable of stimulating proliferation of AA4.1+, Sca-1+, $LIN^{low}$ hematopoietic cells, but have no proliferative effect on AA4.1+, Sca-1+, $LIN^{high}$ hematopoietic cells (see, e.g., 1160-1161). As another example, Lardon *et al.* (Exp. Hematol., 22:903-908, 1994), teach that different subsets of CD34+ cells can respond differently to cytokines. Lardon *et al.* teach three subsets of CD34+ progenitor cells differing in terms of TGF-β responsiveness: 1) progenitor cells stimulated by a combination of IL-3 plus IL-1, SCF, or IL-6 that were arrested specifically in the G1 phase of the second cell cycle; 2) progenitors responding to IL-3 alone that were overall retarded during the first 72 hours after stimulation, without an apparent selective accumulation of cells in any G1

phase; and 3) IL-3-responsive, but TGF-β insensitive, progenitor cells that were not arrested in the second or third cycles. Lardon *et al.* indicate that the kinetic mechanism for the inhibitory effect of TGF-β on the first three cell cycles depends on the stimulus by which the progenitor cells are induced to proliferate. The different stimuli may also trigger different subsets of progenitor cells in terms of maturation stage (see, e.g., pages 907-908, under "Discussion").

In view of the disclosure in the specification of expanding only primitive hematopoietic cells in the presence of media comprising flt-3 ligand, and in view of the state of the art that hematopoietic cell populations at different stages of maturation respond differently to media compositions comprising cytokines, it would have required undue experimentation for one of skill in the art to make and use the invention as claimed without undue experimentation.

Claims 19-26, 29, and 30 are directed to hematopoietic cell expansion media and methods of culturing hematopoietic cells in the expansion media wherein the expansion media comprises a soluble polypeptide that comprises an amino acid sequence that is at least 80% identical to the amino acids 28-160 of SEQ ID NO:6.

The specification teaches that amino acids 28-160 of SEQ ID NO:6 correspond to a soluble form of flt3-L which has the same biological activity as the full length flt3-L (see page 7, lines 18-31 of the specification). In addition, the specification discloses a flt3-L variant which is a polypeptide substantially homologous to native flt3-L but which has an amino acid sequence different from that of native flt3-L because of one or more deletions, insertions or substitutions. The variant amino acid sequence preferably is at least 80% identical to a native flt3-L amino acid sequence, most preferably at least 90% identical (see page 8, lines 5-10 of the specification). However, the specification does not disclose which amino acids in the sequence can be altered such that the flt3-L variant maintains its biological activity, i.e., is capable of binding to its putative receptor. Moreover, a sequence search of the prior art literature and patent literature did not reveal any amino acid sequences of flt3-L having at least 80% identity to flt3-L. Given the lack of disclosure of variant flt3-L sequences which maintain biological activity, and the lack of

such sequences in the prior art literature, the skilled artisan could not envision soluble polypeptides having amino acid sequences which are at least 80% identical to a native flt3-L amino acid sequence.

Given the lack of disclosure of variant flt3-L sequences which maintain biological activity, and the lack of such sequences in the prior art literature, the skilled artisan could not envision soluble polypeptides having amino acid sequences which are at least 80% identical to a native flt3-L amino acid sequence. As the specification does not disclose such variant flt3-L polypeptides, one skilled in the art could not identify which flt3-L polypeptides that are at least 80% identical to a native flt3-L amino acid sequence would have hematopoietic expansion capabilities without undue experimentation.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-18, 27, and 29 are/remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7, 9, and 10 of copending Application No. 08/399,404. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of co-pending application Serial No. 08/399,404 are directed to a kit which comprises a cellular growth medium and a growth factor,

wherein the growth factor can be selected from GM-CSF, G-CSF, IL-1, IL-3, IL-6, TPO, EPO, flt3-ligand, SF, and a GM-CSF/IL-3 fusion protein. As the composition and method of using the composition in the instant application are encompassed in the kit and the intended use of the kit, the claims are not patentably distinct.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-18, 27, and 29 are/remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 59-65 of copending Application No. 08/209,502. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of co-pending application Serial No. 08/209,502 are directed to a cell culture media and a method comprising the step of expanding hematopoietic cells, *in vitro*, using the media, wherein the media of the co-pending application and the instant application encompass the same growth factors. As the composition and method of using the composition in the instant application are encompassed in the media and method of using the media, the claims are not patentably distinct.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant's arguments filed 5/26/00 with respect to the obviousness-type double patenting rejections are acknowledged.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet M. Kerr whose telephone number is (703) 305-4055. Should the

examiner be unavailable, inquiries should be directed to John LeGuyader, Supervisory Primary Examiner of Art Unit 1633, at (703) 308-0447. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 305-7401. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

Janet M. Kerr, Ph.D.
Patent Examiner
Group 1600

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600